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One of these things is not like the other: the heterogeneity of the cerebral circulation

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The human cerebral vasculature is highly sensitive to changes in arterial blood gases (i.e. arterial carbon dioxide (P_{aCO_2}) and oxygen (P_{aO_2}) tensions), such that hypercapnia/hypoxia and hypocapnia/hyperoxia cause global increases and decreases in cerebral blood flow. It is generally accepted that all cerebral arterioles – traditionally considered to be *the* regulators of brain blood flow – are equally sensitive to changes in arterial blood gases. However, this classic dogma may not be the case.

Two independent studies recently published in *The Journal of Physiology* have identified regional differences in cerebral perfusion during acute changes in arterial blood gases (Sato *et al.* 2012; Willie *et al.* 2012). Willie *et al.* (2012) investigated the influence of changes in P_{aCO_2} and P_{aO_2} on blood flow – assessed via blood velocity and vessel diameter – in the extra-cranial internal carotid and vertebral arteries as well as via velocity (only) in the intracranial middle and posterior cerebral arteries. Sato *et al.* (2012) examined the effect of changes in P_{aO_2} (i.e. end-tidal carbon dioxide tension) on blood flow and/or velocity in the internal carotid, external carotid, vertebral, middle cerebral, and basilar arteries. Both studies measured blood flow or velocity using ultrasound techniques. An overview of their findings is presented in Table 1.

Despite technical and methodological differences between these two independent studies, the findings are remarkably complimentary. The data demonstrate that: (1) arterial blood gas sensitivity differs between arteries and the associated downstream vasculature, and (2) this differential sensitivity is readily observable in extra-cranial cerebral perfusing vessels. These findings further our understanding of both cerebrovascular control and reactivity, which will impact future study design and data interpretation. A discussion of these implications follows.

Implications for cerebrovascular control

The findings of these studies potentially shift our understanding of cerebrovascular control in humans. Blood flow through a vascular bed is dictated by perfusion pressure and vascular resistance. In the absence of meaningful changes in perfusion pressure during a perturbation, cerebral perfusion is regulated by changes in resistance primarily at the arterioles. Accordingly, these data show that during *moderate* alterations in arterial blood gases, blood flow changes in the internal carotid and vertebral arteries are mediated by alterations in velocity (Sato *et al.* 2012; Willie *et al.* 2012), presumably via changes in resistance in the downstream arteries as no measurable change in vessel diameter was observed at the insonation location. However, during *severe* hypercapnia, increased internal carotid artery blood flow was at least partially mediated by changes in vessel diameter at the location of insonation, while similar observations were made during *severe* hypoxia in the vertebral artery (Willie *et al.* 2012). These findings indicate that changes in cerebral blood flow upon *severe* changes to arterial blood gases occur through changes in resistance at the level of the extra-cranial cerebral perfusing arteries *and* the arterioles, and thus these changes in resistance are regional and stimulus dependent. How proximal this arterial blood gas sensitivity extends has yet to be determined, though it is clear that not all extra-cranial cerebral arteries are directly sensitive.

That the vertebral artery itself is selectively sensitive to changes in arterial blood gases is an important and perhaps teleologically relevant finding. The P_{aCO_2} reactivity of the vertebra-basilar system (i.e. vertebral and basilar arteries and downstream vasculature) appears to be solely mediated by changes in arteriole resistance (Sato *et al.* 2012; Willie *et al.* 2012), while during hypoxia increases in vertebral artery diameter directly modulate blood flow (Willie *et al.* 2012). Thus, the vertebra-basilar system is selectively sensitive to changes in arterial blood gases such that, relative to their more anterior counterparts, i.e. internal carotid and middle cerebral arteries, this system generally has a reduced sensitivity to P_{aCO_2} (Sato *et al.* 2012) and an enhanced sensitivity to P_{aO_2} (Willie *et al.* 2012). These findings appear to highlight the importance of maintaining blood flow to the vertebra-basilar system, particularly during hypocapnia and hypoxia. By considering the areas of the brain these arteries perfuse, the rationale for a teleological arrangement can be readily hypothesized. That is, the vertebra-basilar system perfuses the posterior brain, an area in which fundamental autonomic structures are positioned, e.g. the brain stem, while the internal carotid and middle cerebral artery arterial tree perfuses a large portion of the cerebral cortex, an area not associated with basic life-supporting functions. Thus, blood flow to the vertebra-basilar system appears to be preferentially maintained during hypocapnia and enhanced during hypoxia. Notably, however, this assertion is speculative, as, for instance, how vertebra-basilar pH is regulated under such circumstances is unknown.

Implications for data interpretation and future study design

Comparing changes in blood flow and/or velocity between arteries appears straightforward, and would be if baseline blood flow and velocity were inherently similar. However, as demonstrated in these studies, blood flow and velocity through the vertebral and basilar arteries, respectively, are consistently lower than the blood flow through the internal carotid artery and velocities in the middle cerebral and posterior cerebral arteries. The traditional manner in which to standardize this is to report a percentage change in blood flow or velocity. Herein lies the problem. Take, for instance, the data from Willie *et al.* (2012) (Fig. 4, p. 3269). The overall sensitivity to changes in P_{aCO_2} in the internal carotid artery was ∼4% mmHg^{-1} or ∼9 ml min^{-1} mmHg^{-1} while in the vertebral artery this sensitivity was ∼4% mmHg^{-1} or ∼3 ml min^{-1} mmHg^{-1}. Subsequently, the conclusions drawn are dependent on

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Table 1. Regional comparisons in cerebrovascular reactivity

P_{aCO_2} reactivity				P_{aO_2} reactivity (Willie *et al.* 2012)		
Extra-cranial			Reference(s)	Extra-cranial		
ICA	>	ECA	Sato *et al.* (2012)	ICA	?	ECA
ICA	> (=)	VA	Sato *et al.* (2012) (Willie *et al.* (2012))	ICA	<	VA
ECA	<	VA	Sato *et al.* (2012)	ECA	?	VA
Intra-cranial			Reference(s)	Intra-cranial		
MCA	=	PCA	Willie *et al.* (2012)	MCA	=	PCA
MCA	>	BA	Sato *et al.* (2012)	MCA	?	BA
PCA	?	BA		PCA	?	BA
Extra-cranial		Intra-cranial	References	Extra-cranial		Intra-cranial
ICA	= (>)	MCA	Sato *et al.* (2012) (Willie *et al.* (2012))	ICA	=	MCA
VA	=	BA	Sato *et al.* (2012)	VA	?	BA

P_{aCO_2}, partial pressure of arterial carbon dioxide; P_{aO_2}, partial pressure of arterial oxygen; ICA, internal carotid artery; ECA, external carotid artery; VA, vertebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; >, higher reactivity; =, equal reactivity; <, lower reactivity; ?, reactivity comparison unknown. The findings from Willie *et al.* (2012) that differed from those presented by Sato *et al.* (2012) are presented in parentheses.

how the data are presented. That is, P_{aCO_2} sensitivity in the vertebral artery could be considered similar (relative) or lower (absolute) to that occurring in the internal carotid artery. Unfortunately, there is no standardized manner to present such data. This represents a significant concern in quantifying regional differences in cerebral perfusion. Therefore, it is important to ascertain under what circumstances relative or absolute measures are physiologically 'relevant'. Even so, by considering the cerebral anatomy, 'relevance' seems to emerge. That is, the middle cerebral artery supplies ∼80% of the blood flow in each hemisphere and the internal carotid (being upstream from the middle cerebral artery) supplies an even larger percentage of the total brain blood flow. This is in contrast to the vertebra-basilar system, which supplies blood to a smaller percentage of the brain. Assuming blood flow is proportional to the brain volume supplied by a given arterial tree, differential absolute sensitivities to the same stimulus would be expected. Therefore, changes in cerebrovascular reactivity should probably be presented relative to the baseline blood flows; however, there is no consensus on this matter. In the meantime, it would be prudent for subsequent studies to heed the recommendation of Willie *et al.* (2012) and report both absolute and relative responses, allowing the reader to interpret the data for themselves.

Both Willie *et al.* (2012) and Sato *et al.* (2012) cleverly utilized ultrasound technology in order to quantify blood flow and velocity. Blood flow was calculated from artery diameter and velocity in the internal carotid, external carotid and vertebral arteries, while in the middle cerebral, posterior cerebral and basilar arteries only blood velocity was measured, as transcranial Doppler cannot measure vessel diameter. Provided artery diameter does not change with alterations in arterial blood gases, changes in velocity provide insight into the magnitude of changes in blood flow. For instance, during moderate hypo- and hypercapnia, middle cerebral artery diameter remains unchanged (Serrador *et al.* 2000), and thus changes in velocity reflect changes in blood flow. However, during *severe* hypercapnia middle cerebral artery diameter increases by almost 10% (Valdueza *et al.* 1999). Data in both studies have been interpreted to provide indirect evidence for changes in intra-cranial artery diameter, such that, during *severe* hypercapnia, changes in intra-cranial blood velocity were consistently underestimated relative to blood flow in their extra-cranial counterparts (Sato *et al.* 2012; Willie *et al.* 2012). However, this interpretation should be carefully considered. That is, unless blood flow for all intra-cranial arteries feeding off a given extra-cranial artery are quantified, changes in intra-cranial blood flow will always be less than blood flow changes in the extra-cranial arteries. Furthermore, the effect of arterial blood gases on the diameter of the basilar and posterior cerebral arteries remains unknown. Therefore, these studies strongly encourage the use and further development of next generation imaging techniques, such as MRI, PET, etc., in discerning the control of the cerebral circulation. Such techniques would allow quantification of intra-cranial blood flow and tissue perfusion, permitting a more complete understanding of regional blood gas sensitivity within the cerebral circulation (e.g. Mandell *et al.* 2008).

The findings of Willie *et al.* (2012) and Sato *et al.* (2012) provide novel insights into the control of brain blood flow. In contrast to the prevailing dogma, these authors have elegantly provided evidence for the heterogeneity of blood flow within the human cerebral circulation. Their data have implications concerning data interpretation and future study design that require consideration. Collectively, these findings highlight the importance of regional blood flow distribution in the chemoreflex control of the cerebrovasculature, and for this, their efforts should be applauded.

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